Neuroendocrine Aspects of the Response to Stress

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Disruptions in homeostasis (ie, stress) place demands on the body that are met by the activation of 2 systems, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Stressor-induced activation of the HPA axis and the SNS results in a series of neural and endocrine adaptations known as the "stress response" or "stress cascade." The stress cascade is responsible for allowing the body to make the necessary physiological and metabolic changes required to cope with the demands of a homeostatic challenge. Here we discuss the key elements of the HPA axis and the neuroendocrine response to stress. A challenge to homeostasis (a stressor) initiates the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which in turn results in release of adrenocortiotropin hormone (ACTH) into general circulation. ACTH then acts on the adrenal cortex resulting in release of a species-specific glucocorticoid into blood. Glucocorticoids act in a negative feedback fashion to terminate the release of CRH. The body strives to maintain glucocorticoid levels within certain boundaries and interference at any level of the axis will influence the other components via feedback loops. Over- or underproduction of cortisol can result in the devastating diseases of Cushing's and Addison's, respectively, but less severe dysregulation of the HPA axis can still have adverse health consequences. These include the deposition of visceral fat as well as cardiovascular disease (eg, atherosclerosis). Thus, chronic stress with its physical and psychological ramifications remains a persistent clinical problem for which new pharmacological treatment strategies are aggressively sought. To date, treatments have been based on the existing knowledge concerning the brain areas and neurobiological substrates that subserve the stress response. Thus, the CRH blocker, antalarmin, is being investigated as a treatment for chronic stress because it prevents CRH from having its ultimate effect—a protracted release of glucocorticoids. New therapeutic strategies will depend on the discovery of novel therapeutic targets at the cellular and intracellular level. Advances in molecular biology provide the tools and new opportunities for identifying these therapeutic targets.

STRESS IS emblematic of 21st century life but defining it in rigorous scientific terms has proven problematic precisely because we all believe we are familiar with it as a term and a state. However, defining stress in a scientific rather than a colloquial or everyday sense is a necessary requirement to begin to unravel the physiological impact stress can have on the body. Unmitigated stress is believed to negatively impact health. Uncontrolled stress is thought to mediate or contribute to problems ranging from cardiovascular damage to compromised cognition due to possible neurodegeneration. Of the 10 leading causes of death, stress has been directly implicated in 4 (heart disease, stroke, musculoskeletal disorders or injuries, and suicide/homicide) and indirectly in 3 (cancer, chronic liver disease, and lung disorders like chronic bronchitis and emphysema).[1-7]

To aid in our discussion of stress we will define stress as any disruption of homeostasis. The maintenance of homeostasis in the face of internal or external challenges, called stressors, requires constant adjustments of a hormonal, behavioral, and autonomic nature. Successfully meeting challenges or allostasis, if excessive, can result in a cumulative physiological burden referred to as "allostatic load."[8] A high load accumulates when the body is required to continuously cope with demands outside the normal operating range. This "wear and tear" caused by high allostatic load can eventually lead to bodily changes that promote disease.[6,9,10] The release of glucocorticoids and catecholamines, crucial integral hormonal mediators of the body's response to stress mounted by the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), respectively, are speculated to play a role in the ability of stress to promote disease. Thus, an understanding of the systems that control the response to stress and the physiological consequences of their actions is an important step in devising strategies to combat the deleterious impact of stress.

THE STRESS RESPONSE

Following disruption of homeostasis, the HPA axis and the SNS are activated. These constitute the essential elements mediating the stress response, all of which are directed towards homeostatic preservation.[11] Here we present an overview of the role of the HPA axis (Fig 1) in the response of the body to stress. Aspects of the stress response related to the SNS are covered in a separate report in this supplement.[12] The HPA axis meets the demands of stress primarily through the synthesis and/or just release of 3 key hormones, corticotropin-releasing hormone (CRH), adrenocorticotropin hormone (ACTH), and a species-specific glucocorticoid, either cortisol (COR) (human, nonhuman primate, swine, and dog) or corticosterone (CORT) (rodents). Other key elements in the stress response are the organs (Fig 1) that release and are acted upon by these hormones. These include the hypothalamic and hippocampal areas of the brain, the anterior pituitary, and the adrenal gland.

A myriad of diverse homeostatic challenges can activate the HPA axis, including cold, infection, hemorrhage, electric shock, vibration, emotional distress, sleep deprivation, social stress, etc.[13,14] The HPA axis is an excellent example of a negative feedback system in which the end product, COR or CORT, "feeds back" and inhibits the production of the initiating substance, CRH. Dysregulation of this negative feedback results in excessive levels of glucocorticoids and is implicated

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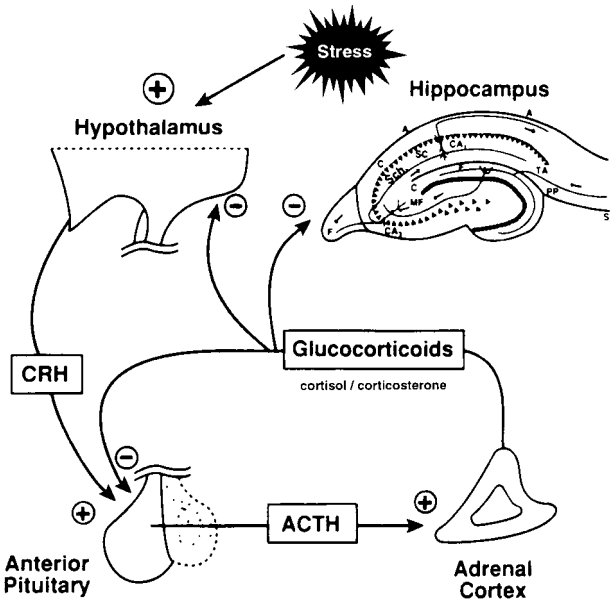

Fig 1. Schematic of the stress cascade. (Adapted with permission from Miller.[79])

in melancholic depression among other disorders.[2,3] An increased number of CRH-expressing neurons found postmortem in the hypothalamus of depressed patients provides anatomical evidence of a dysregulated HPA axis in this disease.[15] Selye[16] was the first to note that chronic exposure to stressors could have pathophysiological consequences such as adrenal hypertrophy, thymic involution, and ulceration of the gastrointestinal tract. Since these initial observations, considerable effort has been devoted to understanding the implications of this pathophysiology for the development of disease.

Any discussion of stress and its consequences is incomplete without a mention of adaptation or habituation. In general, repeated exposure to the same stressor usually results in a loss of the stress response that involves desensitization of elements of the stress pathway to stimulation. The adaptation characteristics are dependent on the type and presentation schedule of the stressor.[17] Interestingly, habituation does not occur for some stressors (eg, repeated foot shock), but if the same stressor is applied repeatedly the application of a new or different stressor usually evokes a potentiated stress response.[17] This sensitization of the HPA axis could actually be considered advantageous for survival because more efficient responding occurs. Continued excretion at elevated levels, however, is likely to be detrimental because glucocorticoid excess would be the ultimate outcome. An understanding of the cellular and molecular changes that control sensitization of the HPA axis are important because pathological sensitization can play a major role in both depression and post-traumatic stress disorders.[18-20] Further, there is evidence that even a single highly traumatic event may produce protracted neuroendocrine sensitization to stress.[18,21,22]

CORTICOTROPIN-RELEASING HORMONE OR FACTOR AND THE ROLE OF THE HYPOTHALAMUS

This highly conserved 41–amino acid neuropeptide was first described by Vale et al.[23] It is primarily responsible for initiation of the stress response by acting through one of its two specific plasma membrane receptors that reside on the corticotrophs of the anterior pituitary.[23,24] What is the source of CRH driving the stress response? Neurons of the paraventricular nucleus (PVN) of the hypothalamus synthesize CRH in response to external and internal stimuli. CRH then travels down the axon projections of these neurons to the external layer of the median eminence. Its subsequent release into portal blood controls ACTH processing in the pituitary corticotrophs. Blocking the actions of CRH with an antibody to this peptide or by a receptor antagonist will prevent the stress-induced release of ACTH.

Approximately 50% to 90% of the PVN neurons projecting to the median eminence contain CRH and are primarily responsible for the release of the CRH that initiates the stress response. Many of the CRH containing neurons of the PVN also express vasopressin (AVP). The removal of the adrenals causes an increased expression of both of these peptides. Expression of both CRH and AVP is under regulatory control by glucocorticoids. Reduction or elimination of glucocorticoids by chemical or surgical removal of the adrenal will result in the upregulation of both CRH and AVP. In some instances, CRH and AVP may act synergistically and augment ACTH release but the biological significance of these interactions is not yet clear. Because CRH and AVP control ACTH production and release through separate receptors and signaling pathways, these synergistic actions may allow rapid and efficient action of the pituitary when circulating glucocorticoid levels are too low.[25] CRH and AVP also are differentially regulated during chronic stress, with CRH expression diminishing as AVP expression increases. This allows ACTH to be released when the organism is exposed to a novel stressor (see Aguilera[17] for a review of the relative roles of CRH and AVP in the stress response).

CRH plays a pivotal integrative role in the response to stress that encompasses initiation, modulation, and inhibition of the stress response. In fact, giving CRH to rats will produce most of the signs associated with exposure to a stressor.[26] CRH may serve as a gatekeeper of the stress response as it is subject to negative feedback on several fronts. Cortisol as well as norepinephrine and gamma-aminobutyric acid shut off the production of CRH.[27] Activation of the CRH receptor leads to the release of ACTH from the pituitary into the general circulation and the ultimate release of glucocorticoids from the adrenal cortex. However, the presence of this neuropeptide and its receptors in the neurons of other brain areas and in organs as diverse as skin, heart, and gastrointestinal tract suggest a multiplicity of functions for CRH.[28,29] There is a high density of CRH receptors in the central nucleus of the amygdala, suggesting a role for CRH in mediating the behavioral response to stress.[30] The presence of a cutaneous CRH pathway may even suggest the functional equivalent of the HPA axis in skin.[28]

What then are the functions of CRH in these other areas? The localization of CRH-containing neurons in brain areas like the hippocampus, amygdala, and cortex, and their formation of

synapses in areas dense with CRH-1 receptors, suggests a role in modulating anxiety, learning and memory. In brain, CRH appears to participate in the regulation of a wide variety of behaviors ranging from motor function to arousal. Animal models of altered CRH signaling have been created through genetic modification. These elegant models are providing insight into the multiple actions of CRH and insight as to how the response to stress can be modulated by excessive or deficient levels of CRH.[31-35]

In healthy humans CRH treatment alters attention, mood, and pain perception.[36-38] CRH injection at appropriate dosages will produce changes in ACTH and cortisol that mimic a stress response. All of these observations lend support to the idea that CRH may be important in mood and anxiety disorders in humans. In the periphery, CRH and its receptors may serve more of a paracrine role by modulating the function of adjacent cells or blood vessels. For example, CRH can induce vascular relaxation and is involved in modulating inflammatory responses.[25]

ADRENOCORTICOTROPIN HORMONE

CRH is delivered to the anterior pituitary and stimulates secretion of ACTH, a 39–amino acid peptide, from resident corticotrophs. ACTH and other neuroactive peptides, such as β-endorphin, are produced by proteolytic cleavage of proopiomelanocortin. ACTH is released into the general circulation and acts on the adrenal cortex, stimulating it to produce glucocorticoids, mineralocorticoids, and adrenal androgens. AVP and catecholamines can augment the response of the pituitary to CRH. At the level of the hypothalamus, ACTH exerts negative feedback control on the production of CRH, which results in the ultimate suppression of ACTH.[39,40] ACTH, along with CRH, plays a major role in orchestrating the response of the body to homeostatic challenge.

GLUCOCORTICOIDS

One consequence of the release of glucocorticoids as a result of the activation of the stress cascade is an elevation in blood glucose. This provides body tissue with the fuel necessary for the increased metabolic demands of an emergency situation. For this reason, glucocorticoids have been called carbohydrate-active steroids, because of their role in carbohydrate metabolism and mobilization of energy stores. Glucocorticoids effect their changes, as does CRH, by binding to specific receptors which are found in every nucleated cell type.[11] The critical nature of having an adequate supply of glucocorticoids is illustrated by the devastating consequences of stress in individuals with adrenal insufficiency (Addisonian crisis) or excess (Cushing's disease). An insufficient supply can produce confusion, lethargy, and circulatory collapse, followed by death.[41] Excess production of glucocorticoids is also problematic with an extreme excess resulting in Cushing's disease. Cushingoid signs are produced by a less severe excess: these include central adiposity and other associated metabolic problems discussed below.[2,42,43]

Glucocorticoids are synthesized from the precursor cholesterol in the zona fasciculata/reticularis zone of the adrenal cortex.[44] The adrenal cortex responds to the pituitary hormone ACTH by releasing species-specific glucocorticoids into the general circulation, via the medullary veins, and to the medullary area of the adrenal itself, via sinusoidal blood. This local delivery of corticosteroids allows hormonal control of epinephrine by regulating the level of the rate-limiting enzyme responsible for the conversion of norepinephrine to epinephrine.

PHYSIOLOGICAL CONSEQUENCES OF HPA AXIS DYSREGULATION

Stress has long been considered to play a role in illness development and is often mentioned as an etiological factor in psychiatric disorders (eg, depression), as well as inflammatory diseases, musculoskeletal disorders, asthma, and heart disease.[45-52] However, the neurobiological mechanisms that link chronic stress or certain stressful events to disease development are not well understood and a clarification of the mechanisms through which stress can engender disease has remained elusive. For example, traumatic life events often precede the development of post-traumatic stress disorder, depression, and schizophrenia. This implicates a role for stress in the pathogenesis of these disorders, although not all individuals exposed to such conditions develop these disorders. Both environmental and genetic factors likely play a role in their development and any determination of the etiological role of stress will need to be considered in the context of constitutional factors specific to the susceptible individuals. Depression, central adiposity, and cardiovascular disease are believed to be specifically related to a dysfunction of the HPA axis and concomitant aberrant production or handling of glucocorticoids, although stress as a rather vaguely defined general concept is often mentioned in conjunction with all of the disorders listed above. The possible role of cortisol in the development of central adiposity and the development of cardiovascular disease is discussed below. An understanding of the general neurobiology of stress and the specific alterations associated with an aberrant handling of glucocorticoids will likely lead to a clarification of the etiological role of stress in disease.[53]

VISCERAL ADIPOSITY, EXCESS CORTISOL, AND CARDIOVASCULAR DISEASE

A hallmark of Cushing's syndrome is the intra-abdominal deposition of fat. The excessive production of cortisol in this disease is believed to be responsible for the skewing of fat storage toward abdominal rather than subcutaneous (gluteofemoral) stores. The relationship between abdominal obesity and excess cortisol in this disease has fueled speculation that chronic stress or dysregulation of the HPA axis with excessive glucocorticoid production may also lead to to central adiposity with its attendant adverse health consequences.[42,43,54-56] HPA axis hyperactivity also is characteristic of many of the genetic models of obesity. Its importance is confirmed by the normalization in weight and fat deposition afforded by removal of the adrenals or blockade of glucocorticoid receptors in these models (see Raber[53] for a discussion). Fat distribution also is normalized in Cushing's syndrome following resolution of excessive cortisol production.

Precisely how excess glucocorticoids control fat deposition is unknown but may be due both to the actions of glucocorti-

coids on adipose tissue as well as a differential sensitivity of certain adipose tissues to these hormones. Because CRH itself has anorexogenic properties, an exaggerated release of cortisol in response to CRH, followed by heightened inhibition of synthesis and/or release of CRH from the hypothalamus, may also play a role in the mishandling of fat associated with excess cortisol.[53-58] Glucocorticoids regulate the differentiation of adipose stromal cells and affect the function of adipocytes. Further, glucocorticoids affect abdominal fat more than subcutaneous adipose tissue. This provides support for the idea that abdominal fat is more likely affected by the excessive production or mishandling of cortisol, as would be expected under conditions of chronic stress. Central adipose tissue has more cells per unit mass, higher blood flow, and more glucocorticoid receptors. Excess glucocorticoids induced by stressful procedures or by their exogenous administration lead to abdominal or visceral fat deposition in rodents.[59] Thus, abdominal obesity in humans may be associated with excessive activity of the HPA axis and can be considered a "functional hypercortisolism."[60]

As Bjorntorp and Rosmond[43] have noted, a high level of visceral fat, as determined by the surrogate measure of waist-to-hip ratio, is a good predictor of disease. Central adiposity is prevalent among men and postmenopausal women and has been found in cross-sectional and prospective studies to be an independent risk factor for cardiovascular disease, type 2 diabetes mellitus, and stroke. High levels of visceral fat are one of the characteristics of the metabolic syndrome X.[58,61] Excessive cortisol due to stress or pharmacological treatment will produce the characteristics of metabolic syndrome X, including visceral obesity, insulin resistance, dyslipidemia, dyscoagulation, and hypertension. Atherosclerosis and cardiovascular disease are the ultimate outcome of this syndrome. Excessive and sustained elevations in cortisol are associated with cardiovascular disease.[1] Patients with Cushing's syndrome often have cardiovascular disease.[62,63] Patients with diagnosed depression have excessive activity of the HPA axis and have a truncated life, apparently due to cardiovascular disease.[64] Workers suffering from "burnout," characterized by the symptoms of emotional exhaustion, physical fatigue, and cognitive weariness, also have elevated cortisol levels and increases in cardiovascular disease risk factors (eg, elevated total cholesterol and triglycerides).[65] Individual differences also determine interactions between stress and the cardiovascular system. The sympathetic nervous system reacts to stress with a release of catecholamines and the degree of sympathetic reactivity can predict the cortisol response engendered by the same stressor, even in healthy individuals. Subjects showing the greatest sympathetic response to a laboratory stressor also show the highest stress-related plasma cortisol level.[66] Whether such laboratory differences in reactivity also are present in response to more natural stressors remains to be determined (see Negrao et al[48] for a discussion).

NEUROHORMONES AS THERAPEUTIC TARGETS—CAVEATS IN THE DEVELOPMENT OF THERAPEUTIC AGENTS

The very complexity of the stress response would appear to provide multiple opportunities for intervention, but treatment strategies are often centered on the amelioration of symptoms rather than attempting to short-circuit the stress response. Further, given the vital physiological nature of the stress response, any pharmacological agent used to ameliorate the consequences of chronic stress must ensure that the body's ability to respond to an acute stressor is not totally eliminated.

Recent efforts have begun to focus on the development of pharmacological agents or other interventions that can alter the stress response itself, rather than the symptoms associated with stress.[1,27] For example, the CRH peptide is a pivotal mediator in the body's response to stress and its dysregulation has been linked to a variety of disorders (eg, depression, post-traumatic stress disorder, bulimia, etc). It has been reasoned that a good strategy for short-circuiting the deleterious effects of stress would be to prevent CRH from having its actions. This is a rational approach to the problem because the administration of CRH can engender most if not all of the repertoire (eg, behavioral, neuroendocrine, autonomic, and neurovegetative) of the body's responses to stress.[26,67-71] As described above, CRH has its actions by binding to the CRH receptor-1 or -2 and pharmacological treatments that prevent or antagonize the effects of this binding might be expected to combat the effects of stress.[26,31]

The development of the pyrrolopyrimidine nonpeptide CRH receptor-1 antagonists, antalarmin, CP 154,526 and R121919, which readily enter the brain, opened a new era for examining the role of CRH in rodent and primate models of stress.[72,73] In rats, antalarmin can block the CRH receptor-1–mediated effects of CRH, including the release of ACTH and various stress behaviors. Further, repeated exposure has no adverse effects on body weight, carbohydrate metabolism, or leptin expression, and it mildly reduces adrenal function without causing atrophy.[31] Perhaps most important is the observation that 8 weeks of exposure to these compounds blunted the basal levels of ACTH and corticosterone but did not impair the ability to respond fully to a novel stressor.[74] Oral administration of antalarmin to primates blocked or reduced the various fear and anxiety behaviors caused by the social stress of exposure to an unfamilar monkey.[75] Treatment also blocked the endocrine responses provoked by the exposure. Such results support the idea that CRH-1 antagonists may have therapeutic value in humans. Depression is a disorder characterized by excessive central CRH activity. The CRH receptor-1 antagonist, R121919, was able to reduce depression and anxiety scores in depressed patients but did not hamper the acute hormonal response to an injection of CRH.[76] This suggests the ability to respond to an acute stressor was not altered by the treatment.

FUTURE DIRECTIONS

Of course the treatments available for preventing or ameliorating the consequences of protracted or excessive stress are dictated by the current state of knowledge concerning the conditions that activate the stress response, as well as the biochemical and physiological consequences of stress for various body systems. The acquisition of knowledge in the areas of genomics and proteomics will accelerate due to the application of existing technologies and the development of new ones. This

will greatly enhance our ability to screen for activation, suppression, or induction of literally thousands of genes and their proteins. Such knowledge will provide new avenues of pursuit for stress treatment strategies. Gene microarray and proteomic technologies will advance our understanding of the effects of stress and provide new directions in stress research and treatment, as they seem likely to do for other complex neurological disorders (eg, schizophrenia).[77,78] Surely, the discovery of novel genomic elements of the stress response will ultimately lead to novel treatments.

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